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MEMORANDUM

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Epoxiconazole Qualitative Risk Assessment Based On Wistar Rat and C57BL/6NCrlBr Mouse Dietary Studies

P.C. Code 123909

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Background

A carcinogenicity study in Wistar rats was conducted by Department of Toxicology, BASF Aktiengesellschaft, Ludwigshafen/ Rhein, Germany, for BASF Corporation, Agricultural Products, Research Triangle Park, North Carolina, and completed July 1992 (Registration Document No. 92/0686; Laboratory Report No. BASF 71S0959/88066; MRID No. 44335017).

The study design allocated groups of 50 rats per sex to dose levels of 0, 30, 150, 750, or 1500 ppm of Epoxiconazole for 105 weeks.

A chronic oral toxicity study in Wistar rats was conducted by Department of Toxicology, BASF Aktiengesellschaft, Ludwigshafen/ Rhein, Germany, for BASF Corporation, Agricultural Products, Research Triangle Park, North Carolina, and completed June 1992 (Laboratory Report No. 92/10685; BASF Project No.

71S0959/88065; MRID No. 44335016).

The study design allocated groups of 20 rats per sex to dose levels of 0, 30, 150, 750, or 1500 ppm of Epoxiconazole for 105 weeks.

Since there were no statistically significant differences in mortality between these studies, they have been combined for the purpose of these analyses.

A carcinogenicity feeding study in C57BL/6NCrlBr mice was conducted by Department of Toxicology, BASF Aktiengesellschaft, Ludwigshafen/ Rhein, Germany, for BASF Corporation, Agricultural Products, Research Triangle Park, North Carolina, and completed July 1992 (Registration Document No. 92/10699; MRID No. 44335018).

The study design allocated groups of 50 mice per sex to dose levels of 0, 0, 1, 5, 200, or 500 (males) or 1000 (females) ppm of Epoxiconazole for 79 weeks. .An additional 10 mice per sex per dose were designated for interim sacrifice at week 53. Since there were no statistically significant differences in mortality between the two control groups, they have been combined for the purpose of these analyses

Survival Analyses

Male and female rats and male mice showed a significant decreasing trend for mortality with increasing doses of Epoxiconazole. The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Epoxiconazole in female mice. See Tables 1 and 2 for rat mortality test results and Tables 11 and 12 for mouse mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 1500 ppm dose group with the controls, for liver carcinomas, adrenal cortex

adenomas, and adrenal cortex adenomas and/or carcinomas combined, all at $p < 0.05$. There was also a significant increasing trend in liver adenomas and/or carcinomas combined at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 150 ppm dose group at $p < 0.05$, and the 50 and 750 ppm dose groups at $p < 0.01$, for pituitary adenomas. There were significant differences in the pair-wise comparisons of the 750 ppm dose group for thyroid follicular cell adenomas, and adenomas and/or carcinomas combined, both at $p < 0.05$. There were significant differences in the pair-wise comparisons of the 150 ppm dose group for thyroid follicular cell carcinomas, and adenomas and/or carcinomas combined, both at $p < 0.01$.

Female rats had significant increasing trends in adrenal cortex adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 1500 ppm dose group with the controls for adrenal cortex adenomas at $p < 0.05$, and for adrenal cortex adenomas and/or carcinomas combined at $p < 0.01$. There were also significant differences in the pair-wise comparisons of the 50 ppm dose group with the controls for liver adenomas, and adenomas and/or carcinomas combined, both at $p < 0.05$. There were significant differences in the pair-wise comparisons of the 50, 750 and 1500 ppm dose groups with the controls for liver cholangiomas, all at $p < 0.05$. There were significant differences in the pair-wise comparisons of the 50 and 150 ppm dose groups with the controls for thyroid c-cell adenomas, and adenomas and/or carcinomas, all at $p < 0.05$. There was also a significant difference in the pair-wise comparison of the 50 ppm dose group with the controls for thyroid c-cell carcinomas at $p < 0.01$, however, this p-value is inflated due to the fact that not all female rats in the 50 ppm dose group were examined for thyroid c-cell tumors. There was a significant increasing trend, and significant differences in the pair-wise comparisons of the 750 and 1500 ppm dose groups with the controls, for ovarian granulosa cell tumors, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 150, 750 and 1500 ppm dose groups with the controls for ovarian luteomas, all at $p < 0.05$.

Male mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 500 ppm dose group with the controls, for kidney transitional cell

papillomas, both at $p < 0.01$. There were significant increasing trends in liver adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 500 ppm dose group with the controls for liver adenomas at $p < 0.05$, and for carcinomas, and adenomas and/or carcinomas combined, both at $p < 0.01$.

Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1000 ppm dose group with the controls, for liver adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p < 0.01$.

The statistical analyses of the male and female rats and the male mice were based upon Peto's prevalence test. The Exact trend test and the Fisher's Exact test for pair-wise comparisons was used for the analyses of the female mice. See Tables 3 - 10 for rat tumor analysis results, and Tables 13 - 16 for mouse tumor analysis results.

Table 1. Epoxiconazole - Wistar Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-26	27-52	53-78	79-106[f]	Total
0	0/70	0/70	6/70	14/64	20/70 (29)**[n]
50	0/70	1/70	3/69	12/66	16/70 (23)
150	0/70	1/70	4/69	14/65	19/70 (27)
750	0/70	1/70	1/69	9/68	11/70 (16)
1500	0/70	0/70	0/70	8/70	8/70 (11)**[n]

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 105.

[n]Negative trend or negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Epoxiconazole - Wistar Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-26	27-52	53-78	79-108[f]	Total
0	1/70	2/69	2/67	22/65	27/70 (39) *[n]
50	0/70	0/70	4/70	22/66	26/70 (37)
150	0/70	0/70	1/70	15/69	16/70 (23)
750	1/70	1/69	1/68	10/67	13/70 (19) *[n]
1500	1/70	0/69	4/69	11/65	16/70 (23)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 105.

[n]Negative trend or negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Epoxiconazole - Wistar Rat Study

Male Adrenal Cortex Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Adenomas (%)	2/60 (3)	3[a]/61 (5)	3/62 (5)	5/66 (8)	7/67 (10)
p =	0.020*	0.387	0.365	0.153	0.047*
Carcinomas (%)	0/59 (0)	1[b]/59 (2)	0/62 (0)	1/65 (2)	0/67 (0)
p=	0.541	0.098	-	0.179	-
Combined (%)	2/60 (3)	4/61 (7)	3/62 (5)	6/66 (9)	7/67 (10)
p =	0.023*	0.242	0.365	0.097	0.047*

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 91, dose 50 ppm.

[b]First carcinoma observed at week 94, dose 50 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Epoxiconazole - Wistar Rat Study

Male Liver Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Adenomas (%)	16[a]/60 (27)	9/61 (15)	6/62 (10)	13/66 (20)	18/67 (27)
p =	0.111*	-	-	-	-
Carcinomas (%)	3[b]/62 (5)	4/63 (6)	4/64 (6)	3/66 (5)	10/69 (14)
p=	0.013*	0.427	0.381	0.456	0.040*
Combined (%)	19/62 (31)	13/63 (21)	9[c]/64 (14)	16/66 (24)	27[c]/69 (39)
p =	0.007**	-	-	-	0.221

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 91, dose 0 ppm.

[b]First carcinoma observed at week 87, dose 0 ppm.

[c]One animal in each of the 150 and 1500 ppm dose groups had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Epoxiconazole - Wistar Rat Study

Male Thyroid Follicular Cell Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Adenomas (%)	1/57 (2)	0/4 (0)	0/8 (0)	2[a]/11 (18)	4/66 (6)
p =	0.096	-	-	0.022*	0.129
Carcinomas (%)	1/50 (2)	0/2 (0)	1/1 (100)	0/6 (0)	1[b]/62 (2)
p=	0.732	-	0.000**	-	-
Combined (%)	2/57 (4)	0/4 (0)	1/8 (12)	2/11 (18)	5/66 (8)
p =	0.234	-	0.000**	0.046*	0.190

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 98, dose 750 ppm.

[b]First carcinoma observed at week 105, dose 1500 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Epoxiconazole - Wistar Rat Study

Male Pituitary and Prostate Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Pituitary Adenomas (%)	26/68 (38)	16[a]/29 (55)	16/29 (55)	17/25 (68)	32/70 (46)
p =	0.854	0.005**	0.012*	0.001**	0.328
Prostate Adenomas (%)	1/70 (1)	0/17 (0)	0/21 (0)	0/17 (0)	5[b]/70 (7)
p=	0.062	-	-	-	0.079

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First pituitary adenoma observed at week 63, dose 50 ppm.

[b]First prostate adenoma observed at week 105, dose 1500 ppm.

Note: There were no pituitary or prostate carcinomas observed.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Epoxiconazole - Wistar Rat Study

Female Adrenal Cortex Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Adenomas (%)	3/56 (5)	3[a]/60 (5)	2/62 (3)	3/62 (5)	11/60 (18)
p =	0.001**	-	-	-	0.012*
Carcinomas (%)	0/43 (0)	0/44 (0)	0/54 (0)	0/56 (0)	2[b]/54 (4)
p=	0.009**	-	-	-	0.102
Combined (%)	3/56 (5)	3/60 (5)	2/62 (3)	3/62 (5)	13/60 (22)
p =	0.000**	-	-	-	0.005**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 95, dose 50 ppm.

[b]First carcinoma observed at week 105, dose 1500 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. Epoxiconazole - Wistar Rat Study

Female Liver Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Adenomas (%)	2/66 (3)	8[a]/67 (12)	0/69 (0)	2/67 (3)	2/65 (3)
p =	0.849	0.027*	-	-	-
Carcinomas (%)	0/43 (0)	0/44 (0)	3[b]/54 (6)	0/57 (0)	0/54 (0)
p=	0.876	-	0.059	-	-
Combined (%)	2/66 (3)	8/67 (12)	3/69 (4)	2/67 (3)	2/65 (3)
p =	0.925	0.027*	0.421	-	-
Cholangiomas (%)	0/53 (0)	3[c]/56 (5)	3/59 (5)	4/61 (7)	5/59 (8)
p=	0.054	0.044*	0.059	0.039*	0.021*

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 77, dose 50 ppm.

[b]First carcinoma observed at week 105, dose 150 ppm.

[c]First cholangioma observed at week 97, dose 50 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. Epoxiconazole - Wistar Rat Study

Female Thyroid C-Cell Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Adenomas (%)	8[a]/65 (12)	3/24 (12)	4/18 (22)	2/13 (15)	11/65 (17)
p =	0.662	0.042*	0.028*	0.094	0.357
Carcinomas (%)	0/43 (0)	1[b]/2 (50)	0/3 (0)	0/3 (0)	0/54 (0)
p=	0.846	0.000**	-	-	-
Combined (%)	8/65 (12)	3[c]/24 (12)	4/18 (22)	2/13 (15)	11/65 (17)
p =	0.662	0.042*	0.028*	0.094	0.357

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 79, dose 0 ppm.

[b]First carcinoma observed at week 107, dose 50 ppm.

[c]One animal in the 50 ppm dose group had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 10. Epoxiconazole - Wistar Rat Study

Female Ovarian and Uterine Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	150	750	1500
Ovarian Granulosa Cell Tumors (%)	2/60 (3)	4/62 (6)	3/65 (5)	13[a]/66 (20)	16/61 (26)
p =	0.000**	0.137	0.294	0.003**	0.001**
Ovarian Luteomas (%)	0/55 (0)	0/57 (0)	3[b]/60 (5)	4/63 (6)	3/60 (5)
p=	0.051	-	0.039*	0.039*	0.033*
Uterine Adenomas (%)	0/43 (0)	2[c]/44 (5)	0/54 (0)	0/57 (0)	3/54 (6)
p =	0.064	0.080	-	-	0.059

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First ovarian granulosa cell tumor observed at week 88, dose 750 ppm.

[b]First ovarian luteoma observed at week 96, dose 150 ppm.

[c]First uterine adenoma observed at week 105, dose 50 ppm.

Note: There were no uterine carcinomas observed.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 11. Epoxiconazole - C57BL/6NCrlBr Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-26	27-52	52[i]	53-82[f]	Total
0	2/120	1/118	20/117	36/97	39/100 (39)**[n]
1	0/60	3/60	10/57	17/47	20/50 (40)
5	0/60	2/60	10/58	14/48	16/50 (32)
200	0/60	0/60	10/60	6/50	6/50 (12)**[n]
500	0/60	0/60	10/60	8/50	8/50 (16)**[n]

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 52.

[f]Final sacrifice at week 79.

[n]Negative trend or negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 12. Epoxiconazole - C57BL/6NCrlBr Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-26	27-52	53[i]	53-81[f]	Total
0	3/120	5/117	19/112	29/93	37/101 (37)
1	1/60	1/59	10/58	14/48	16/50 (32)
5	2/60	1/58	9/57	13/48	16/51 (31)
200	2/60	1/58	8/57	12/49	15/52 (29)
1000	0/60	2/60	9/58	20/49	22/51 (43)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 79.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 13. Epoxiconazole - C57BL/6NCrlBr Mouse Study

Male Liver Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	1	5	200	500
Adenomas (%)	0/61 (0)	0/30 (0)	0/34 (0)	0/44 (0)	3[a]/42 (7)
p =	0.001**	-	-	-	0.018*
Carcinomas (%)	1/86 (1)	0/40 (0)	0/46 (0)	3/48 (6)	33[b]/50 (66)
p=	0.000**	-	-	0.087	0.000**
Combined (%)	1/86 (1)	0/40 (0)	0/46 (0)	3/48 (6)	34[c]/50 (68)
p =	0.000**	-	-	0.087	0.000**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 81, dose 500 ppm.

[b]First carcinoma not in an interim sacrifice animal observed at week 69, dose 500 ppm.

[c]Two animals in the 500 ppm dose group had both an adenoma and a carcinoma.

Note: One animal in the interim sacrifice group of the 5 ppm dose group had a carcinoma. There were no adenomas in any interim sacrifice animals. Interim sacrifice animals are not included in this analysis.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 14. Epoxiconazole - C57BL/6NCrlBr Mouse Study

Male Kidney and Lymphoma Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	1	5	200	500
Kidney Transitional Cell Papillomas (%)	3[a]/87 (3)	1/42 (2)	1/46 (2)	1/48 (2)	7/50 (14)
p =	0.000**	-	-	-	0.003**
Malignant Lymphoma (all sites) (%)	33[b]/120 (28)	14/60 (23)	15/60 (25)	13/60 (22)	20/60 (33)
p =	0.475	-	-	-	0.466

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First kidney transitional cell papilloma observed at week 68, dose 0 ppm.

[b]First malignant lymphoma (all sites) observed at week 26, dose 0 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 15. Epoxiconazole - C57BL/6NCrlBr Mouse Study

Female Liver Tumor Rates* and Exact Trend Test
and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	1	5	200	1000
Adenomas (%)	0/93 (0)	0/46 (0)	0/48 (0)	0/49 (0)	5[a]/49 (10)
p =	0.000**	1.000	1.000	1.000	0.004**
Carcinomas (%)	1/93 (1)	1/46 (2)	1/48 (2)	1/49 (2)	33[b]/49 (67)
p=	0.000**	0.554	0.567	0.573	0.000**
Combined (%)	1/93 (1)	1/46 (2)	1/48 (2)	1/49 (2)	38/49 (78)
p =	0.000**	0.554	0.567	0.573	0.000**

*Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 65, dose 1000 ppm.

[b]First carcinoma not in an interim sacrifice animal observed at week 56, dose 1000 ppm.

Note: One animal in the interim sacrifice group of the 1000 ppm dose group had a carcinoma. There were no adenomas in any interim sacrifice animals. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 16. Epoxiconazole - C57BL/6NCrlBr Mouse Study

Female Kidney Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	1	5	200	1000
Adenomas (%)	4/93 (4)	4/46 (9)	1[a]/48 (2)	4/49 (8)	4/49 (8)
p =	0.191	0.249	0.444[n]	0.279	0.279
Carcinomas (%)	0/93 (0)	1/46 (2)	1/48 (2)	1[b]/49 (2)	0/49 (0)
p=	0.490	0.331	0.340	0.345	1.000
Combined (%)	4/93 (4)	5/46 (11)	2/48 (4)	5/49 (10)	4/49 (8)
p =	0.282	0.134	0.669	0.156	0.279

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 59, dose 5 ppm.

[b]First carcinoma observed at week 75, dose 200 ppm.

[n]Negative change from control.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Chemical:	**(2RS, 3SR)-3-(2-chlorophenyl)-2-(4-fluor**
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